

Growth and growth charts in cystic fibrosis

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INTRODUCTION

Growth is a dynamic process that starts at conception and ends after full pubertal development. The assessment of growth in children with cystic fibrosis (CF) is essential for monitoring well being, disease activity and response to treatment. We explain how growth is assessed and review the literature on growth in children with CF. We searched the literature for key terms (referring to somatic growth, growth impairment, puberty and delayed puberty in cystic fibrosis) using the databases of MEDLINE (National Library of Medicine) and EMBASE (Excerpta Medica) from 1 January 1950 to 31 January 2003. The bibliographies of identified papers were also examined.

Box 1 Principles of measuring weight, height and length

Weight

- Scales accurately calibrated and reliable
- Child weighed wearing minimum of clothing and infant without nappy
- Weight recorded to nearest 100 g

Height

- Height meter correctly installed and accurately calibrated
- Child measured without shoes and socks
- Child stands with heels flat and together, legs straight and shoulders relaxed, heels, buttocks and scapulae against the wall, eyes looking straight ahead and in the same plane as the external auditory meati
- Child is asked to breathe in
- Gentle but firm upward pressure is exerted on the mastoid processes as the child breathes out and relaxes
- Height is read to the nearest mm

Length (under 2 years age)

- Two people are required: one person ensures head is correctly positioned and in contact with the headboard and other person ensures back and legs are straight and feet are flat against the footboard.

ASSESSMENT OF GROWTH IN CHILDREN WITH CF

In clinical practice, the assessment of growth means: (1) measuring weight and height (length in children <2 years age) accurately at regular intervals (≤ 3 months apart); (2) carefully plotting measurements on appropriate standard growth charts, such as those described by Freeman *et al.* for the UK;¹ and (3) correctly interpreting the measurements. The measurements should be made with accurately calibrated and reliable equipment and children correctly positioned (see Box 1). Serial measurements of a child should be plotted on the same standard growth chart ('distance charts' with measurements of height and weight plotted against age) at each assessment (Figure 1).¹ Interpretation requires comparing weight in relation to height, and comparing the measurements with previous measurements

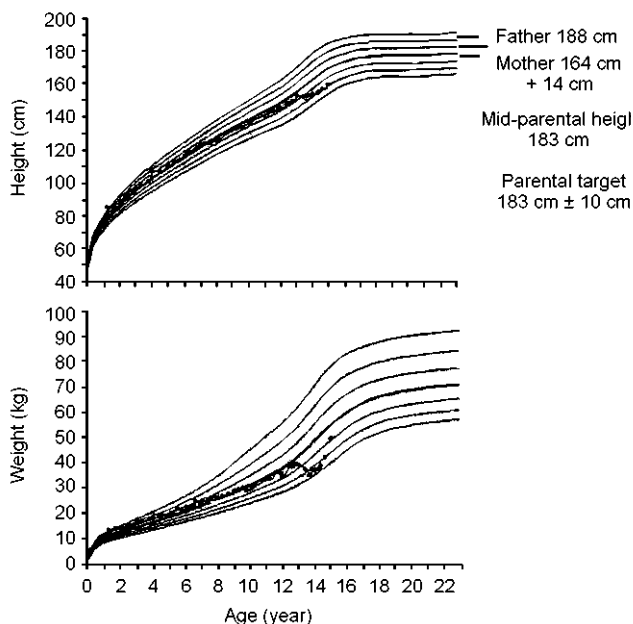


Figure 1 Standard distance charts of height and weight plotted against age. The normal centile lines are shown in grey (2nd, 9th, 25th, 50th, 75th, 91st and 98th). Serial measurements of a 15-year-old boy with cystic fibrosis (CF) have been plotted. He had airway colonization with *Pseudomonas aeruginosa* from 10 years of age (FEV₁ 84% of predicted). The dramatic decline in weight between 13.5 to 14.5 years of age was associated with exacerbation of respiratory symptoms, fall in FEV₁ to 44% predicted and the patient being quiet and 'withdrawn'. His height trajectory closely followed the 50th centile until around 10 years of age. During the period of poor weight gain, he had growth failure and his height dropped to the 9th centile. Parents' heights are plotted on the right side of the chart

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Table 1 Plotting parental heights on distance charts and determining adult target range

For a boy		For a girl
Father's height (cm)	Plot height	Plot (height – 14 cm)
Mother's height (cm)	Plot (height+14 cm)	Plot height
Mid-parental height (cm)	$\frac{\text{Father's height} + (\text{mother's height} + 14)}{2}$	$\frac{(\text{Father's height} - 14) + \text{mother's height}}{2}$
Adult target range (cm)	Mid-parental height ± 10 cm	Mid-parental height ± 8.5 cm

and progression with the chart centiles. In addition, the measurements need to be interpreted in the context of pubertal status and parents' measurements (Table 1).

Growth charts are derived from measurements of a large number of healthy children. For every variable measured, such as height, the values at each age are ranked into 100 equal parts using statistical methods. A select number of these ranks or percentiles (e.g. 0.4th, 2nd, 9th, 25th, 50th, 75th, 91st, 98th and 99.6th for the current UK charts¹) are plotted as curves against age to produce growth percentile charts. Such percentile charts help to describe and compare the position of measurements from a patient in relation to healthy children.

A histogram of the measurements from healthy children for a variable such as height will reveal a symmetrical bell-shaped normal distribution. According to the empirical rule, approximately 95% of the measurements are within two standard deviations of the mean (i.e. between the 2.3rd and 97.7th percentiles). In other words

- only 5% of measurements from healthy children fall outside the range between -2 and $+2$ standard deviations
- the measurement of a particular child is more likely to be abnormal than normal if it falls below -2 standard deviations (i.e. below the ~ 2 nd percentile) or above $+2$ standard deviations (i.e. above the ~ 98 th percentile).

There is no strict division between normal and abnormal, but this way of interpreting a measurement gives a probability of whether it is normal or abnormal. Definitions of terms used to describe abnormal growth are presented in Box 2.

The growth rate as well as the characteristic pattern of normal growth are illustrated by the percentile lines on standard distance growth charts¹ (see Figure 1). Before puberty, the line of growth of a 'healthy' child with a normal growth rate is parallel to the percentile lines on these charts. Changes in the growth rate serve as pointers to health problems: a slow rate of growth is indicated by a child's line of growth deviating down and crossing lower percentile lines while a fast rate of growth (as seen with catch-up growth) is suggested by the reverse. For precision,

Box 2 Some useful definitions of terms used to describe abnormal growth

Failure to thrive

- Failure to fulfil potential in terms of physical, social and emotional growth and development. In the somatic sense, this means failure of an infant/preschool child to gain weight at an appropriate rate

Undernutrition

- Percentage weight for height 85–90%

Malnutrition

- Percentage weight for height $< 85\%$

Underweight

- Weight below a cut-off value, e.g. 2nd centile
- Drop in weight centile from maximum centile at 4–8 weeks age and remaining at lower centile for ≥ 1 month

Short stature

- Height below a cut-off value, e.g. 2nd centile. This does not necessarily mean that it is abnormal

Growth failure

- Failure to achieve height velocity appropriate for age and stage of puberty (a height velocity between the 25th and 75th centiles is generally considered normal). This means a drop in height centile with serial measurements and the line of growth is not parallel to the standard centile lines on a height distance chart

Catch-up growth

- Height velocity above normal limits for age and stage of puberty during a defined period of time, following a transient period of growth inhibition

Delayed puberty

- Late onset of puberty (> 15 years in boys; > 14 years in girls) or attenuated progress through puberty.

the rate of growth (i.e. velocity) can be calculated from serial measurements taken 12 months apart and interpreted by plotting on 'velocity charts'² (Figure 2).

Additional methods of interpreting a child's growth measurements include expressing them as standard deviation

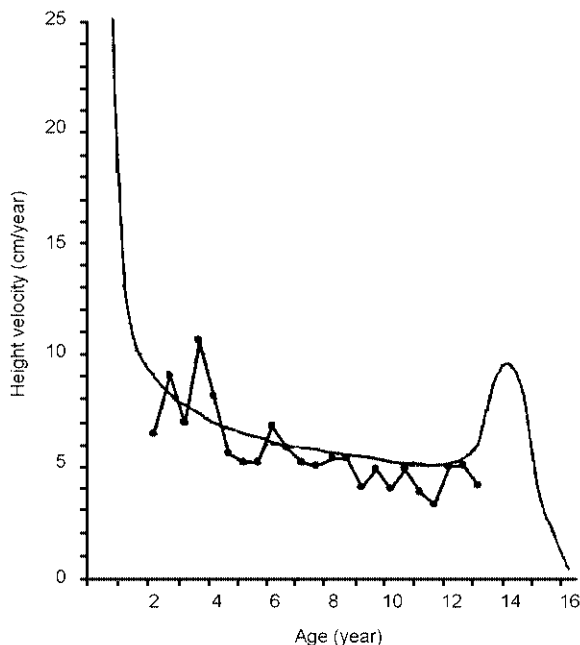


Figure 2 Height velocity chart of the patient described in Figure 1. The 50th centile line for the normal population is shown in grey. The patient's height velocity, calculated from height measurements taken 12 months apart, has been plotted

scores (or Z scores) or as a percentage of the normal values for age. Percentage weight for height is often used to assess the nutritional status of children with CF (Figure 3).³

GROWTH AND PUBERTY IN CHILDREN WITH CF

Reduced weight at birth of infants with CF compared to unaffected infants (250 gm less on average) was reported in the 1950s.^{4,5} Except for those with meconium ileus, the majority of infants with CF were asymptomatic at birth and this raised the possibility of prenatal and genetic influences on growth.⁵ Failure to thrive is one of the presenting features of CF after the neonatal period, and poor weight gain and linear growth from birth until the time of diagnosis are well recognized.^{6,7} Lai *et al.* found approximately 40% of infants were below the 5th percentile for weight and length at diagnosis.⁷ They observed some catch-up growth after infancy, possibly associated with aggressive management following diagnosis, and a smaller proportion of their patients (20–25%) had weight and length below the 5th percentile at 2 years of age. Others have also reported catch-up growth after diagnosis.^{6,8–10}

Despite the catch-up growth observed after diagnosis, better management and nutritional support, deficits in length/height and weight continue to be seen until adulthood.^{6–10} Of the 13 116 children with CF in the US studied by Lai *et al.*, around one-third were below the 10th percentile and less than 25% were above the 50th percentile for height and weight.⁷ In one study, the median heights

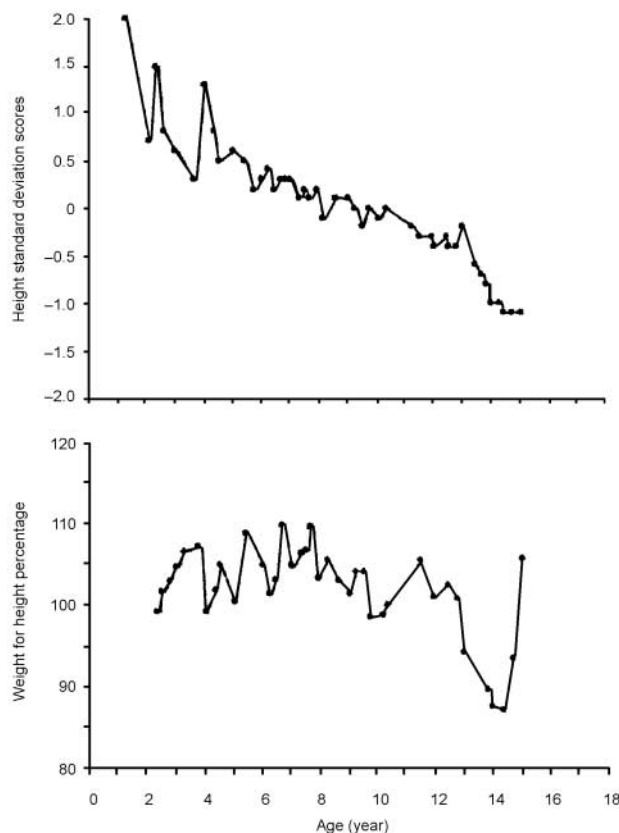


Figure 3 Charts showing height standard deviation scores (SDS or Z scores) and weight for height percentage plotted against age of the patient described in Figure 1. Note the decline in height SDS from around 0 at 10 years age to less than -1 SDS at 15 years' age. There has been a catch-up in weight for height between 14 and 15 years age

and weights of 50 patients with CF did not exceed the normal 10th percentile at any age.⁸ Although their weight and height were on lower percentiles, 89% of these children had a normal growth pattern under 9 years of age. The Wisconsin CF Neonatal Screening Project found better growth during the 13 years of the study in patients diagnosed early with screening compared to the control group who were diagnosed by a positive family history or clinical features of CF (mean age at diagnosis 13 versus 100 weeks).¹¹ From a cross-sectional survey of 3056 patients with CF in the UK, Morison *et al.* constructed reference percentile charts for weight, height and body mass index (BMI) for males and females.¹⁰ They noted weight was approximately 0.5 standard deviations below the population mean between 1 to 10 years age and deviated further thereafter. BMI declined in boys after 10 years age and in girls after 5 years age.

The growth impairment in patients with CF is recognized to be more severe during adolescence than in mid-childhood and the prepubertal years (10–25th percentiles).^{6–10,12} This is associated with a delay in skeletal maturation, onset of puberty, the pubertal growth spurt and

attaining adult height.¹³ Sproul *et al.* found bone age was delayed by more than 24 months in a quarter of the adolescents with CF.⁸ Compared to normal children, delay in age at peak height velocity by 9–10 months in boys and 10–14 months in girls has been noted in CF patients.^{12,14,15} A negative relationship between age at peak height velocity and peak height velocity has been observed and patients with extreme delay in puberty fail to demonstrate a significant growth spurt.¹⁴ Peak height velocity is attenuated in subjects with constitutional delay in growth and puberty and has been found to be even lower in patients with CF (by 0.7–1.8 cm/year in girls and 1 cm/year in boys).^{14,15} Consequently, the adult height of CF patients is reduced and corresponds to 25–42nd percentiles for males and 25–44th percentiles for females.^{6,12,14,16,17} Menarche has also been found to occur later in girls with CF (14.2–14.9 years versus 12.9–13.1 years in healthy girls).^{6,12,14,15,18–20}

FACTORS CONTRIBUTING TO GROWTH IMPAIRMENT AND DELAYED PUBERTY IN CHILDREN WITH CF

Numerous factors are likely to contribute to growth impairment and delayed puberty in children with CF and the most important are undernutrition (from malabsorption, inadequate intake and increased requirements), chronic inflammation and lung disease, and oral/inhaled corticosteroid treatment (Box 3). Undernutrition, growth failure and poor lung function are closely related and a number of studies illustrate the positive effects of aggressive nutritional intervention on growth.^{16,21–23} Differences in growth and survival, possibly related to differences in nutritional management (low fat, high calorie diet and lower dose of pancreatic enzymes versus high fat, high calorie diet and higher dose of pancreatic enzyme treatment) have been described between 499 CF patients in Boston and 534 patients in Toronto.¹⁶ Boston patients were shorter between ages 10 to 25 years and the males had lower weight percentiles (mean 35th versus 43rd percentile) compared to Toronto patients. Although FEV₁ did not differ between the two centres, median survival was 21 years in Boston and 30 years in Toronto. Factors that need to be taken into consideration for any trends which show poor or worse growth over time are the progressive nature of the disease and longer survival of patients with more severe disease.²⁴

Lai *et al.* studied the growth of 32 patients with meconium ileus and 50 without meconium ileus who were diagnosed through neonatal screening before 12 weeks age to eliminate the effects of impaired growth prior to diagnosis seen in patients who present with symptoms.^{25–27} The patients without meconium ileus achieved near normal growth from birth to 12 years age. In contrast, those with meconium ileus had significant growth impairment from

Box 3 Factors likely to contribute to growth impairment in cystic fibrosis

Malabsorption and other excessive losses

- Pancreatic insufficiency: evolving pancreatic damage, delayed diagnosis, inappropriate enzyme replacement, noncompliance with pancreatic enzyme replacement therapy
- Low pH in the small intestine
- Impaired bile salt production
- Short gut: intestinal resection
- Gastro-oesophageal reflux
- Salt depletion and pseudo-Bartter's syndrome
- Coexisting diseases: coeliac disease, inflammatory bowel disease

Anorexia and/or inadequate calorie intake

- Medication causing anorexia, nausea or abdominal pain
- Eating behaviour problems: milk refusal, fussy eater, psychological problems

Increased energy expenditure

- Normal and catch-up growth
- Chronic inflammation, lung disease and catabolic state

Others

- Diabetes mellitus
- Liver disease
- Systemic and/or inhaled corticosteroid treatment
- Physical changes such as postural abnormalities, osteoporosis

birth and mean weight and height across all ages were around the 30th percentiles. Growth was more impaired in the infants who had surgery, but was not influenced by intestinal resection nor due to poor dietary intake. However, patients with meconium ileus had abnormal plasma essential fatty acid status with low levels of linoleic acid which correlated with height percentile. Low levels of linoleic acid were also reported by Johannesson in adolescent girls with CF and these studies propose an influence of essential fatty acid status on growth and puberty.¹⁵

In contrast to the study by Johannesson, Moshang *et al.* observed that girls with CF were shorter (mean height 156.4 versus 158.5 cm), lighter (mean weight 43.8 versus 47.8 kg) and had lower estimated body fat (mean 20.1 versus 23.5%) at menarche than healthy girls.^{15,18} Importantly, in both studies, 20% of the girls with CF achieved menarche despite failing to reach the critical body fat of 17% and weight of 47.8 kg, indicating that factors other than nutritional status influence puberty in CF.²⁸ Like Byard, Johannesson *et al.* found a greater delay in puberty in girls homozygous for $\delta F508$ than girls with other CF

mutations, and speculated an effect of mutated cystic fibrosis transmembrane regulator in the brain on neuroendocrine secretion.^{14,15} However, this has not been supported by other investigators.²⁹

A number of studies have illustrated the variations in growth in individual children with CF from one time to another.^{8,30} Greco and co-workers observed peaks and lags in height and weight velocities of children with CF measured at 3-monthly intervals and noted that 71–82% of adverse clinical events (mainly respiratory and gastrointestinal complications) were related to lags in growth velocities.³⁰ Examining the growth patterns of 50 patients, Sproul and Huang found all episodes of growth failure in children younger than 9 years old and 60% of episodes in the older patients were associated with active lung disease.⁸ Other investigators have reported the negative influence of severity of lung disease and airway colonization with *Pseudomonas aeruginosa* on growth and onset of puberty in children with CF.^{8,14,18,31}

It is likely that the major factors that impair growth, such as undernutrition, chronic inflammation and corticosteroid treatment, do so by attenuating the functional integrity of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis through complex interactions. Normal spontaneous and stimulated GH levels but low levels of IGF-I and IGFBP-3 (the principal binding protein) in children with CF suggest a state of relative GH insensitivity.^{32,33} Both IGF-I and IGFBP-3 levels have been observed to correlate with height and BMI as a marker of nutritional state, as well as decline with age, in parallel to the fall in BMI with increasing age.³³ Recent evidence from an animal model and from children with juvenile chronic arthritis suggests that an interleukin-6 mediated decrease in IGF-I may be an important mechanism by which growth is impaired in chronic inflammatory conditions, independent of nutrition.^{34,35} While high circulating levels of the pro-inflammatory cytokines interleukin-6 and tumour necrosis factor- α have been reported from patients with CF,^{36–38} the link between these, low levels of IGF-I and impaired growth has not yet been investigated.

An association between delayed puberty in girls with impaired oral glucose tolerance test without overt diabetes has been described, and Ripa and co-workers have reported the influence of insulin deficiency on growth in 18 children with CF aged 9.5 to 15 years.^{15,30} Their patients were shorter (mean height -0.52 standard deviation score), growing slower than expected for age (nine patients had height velocity <25 th percentile) and had mild to moderate lung disease. Twenty per cent had undiagnosed impaired glucose homeostasis and 65% had impaired insulin secretion (assessed from the sum of the plasma insulin values at 1 and 3 minutes of the intravenous glucose tolerance test). There was no relationship between glucose

levels during the oral glucose tolerance test and growth rate. Plasma insulin area under curve correlated strongly with height velocity even when adjusted for age, suggesting that declining insulin secretion may contribute to poor linear growth. There was also a significant association between plasma insulin area under curve and serum IGFBP-3, and patients whose insulin secretion was most impaired (<1 st percentile) had lower serum IGFBP-3 levels but higher IGFBP-1 levels than normal controls. Thus insulin deficiency may adversely affect growth by disturbing the GH/IGF-I axis as a result of reduced levels of IGFBP-3 and increased levels of inhibitory IGFBP-1. In addition, it may contribute to the delay in puberty by impairing gonadotrophic activity and steroidogenesis in the ovaries.⁴⁰

Reactivation of the hypothalamic gonadotrophin releasing hormone (GnRH) pulse generator is thought to be critical for the normal physical transition from prepuberty to puberty.⁴¹ A negative influence on this as a result of undernutrition, chronic illness and corticosteroid treatment offers another explanation for the delay in the onset of puberty seen in some patients with CF. This is supported by the absence of significant abnormalities in gonadotrophin and sex steroid levels in prepubertal and pubertal children with CF compared to otherwise healthy children and children with constitutional delay in growth and puberty.^{18,42}

RECOMBINANT HUMAN GH TREATMENT IN CHILDREN WITH CF

Owing to a state of relative GH insensitivity, the anabolic and growth promoting effects of recombinant human IGF-I (rhIGF-I) and GH (rhGH) treatment have been explored in children with CF. We are only aware of one placebo controlled trial of rhIGF-I treatment for 6 months in seven CF patients which found an increase in IGF-I levels but no effects on linear growth and weight gain with rhIGF-I treatment.⁴³ Its tendency to induce hypoglycaemia may be beneficial in patients with impaired glucose tolerance but detrimental for those with normal glucose homeostasis. However, the major limitation of treatment is the lack of availability of rhIGF-I.

A number of open-labelled uncontrolled studies of small numbers of undernourished prepubertal children with CF documented improvements in weight and height with rhGH treatment for up to 2 years.^{44–49} The National Cooperative Growth Study included 24 patients with CF treated with rhGH and two patients developed impaired glucose tolerance over 2 years.⁴⁴ In a randomized controlled trial over 1 year of 19 prepubertal patients whose initial height and weight were ≤ 10 th percentile despite adequate calorie intake, Hardin *et al.* reported greater height velocity (8.1 versus 3.8 cm/year), weight velocity (4.5 versus 2.1 kg/year) and increase in lean mass (4.7 versus 2.1 kg) in those

who had rhGH compared to those who did not.⁵⁰ A randomized cross-over trial with rhGH treatment for 6 months also supported these findings.⁵¹ Further observations by Hardin *et al.* suggest that the improvements in growth and lean mass with rhGH might be due to improved whole body protein catabolism and improved efficiency of whole body protein kinetics.⁵² Significant clinical benefits were also observed in the rhGH treated patients with increase in forced vital capacity, reduced number of hospital admissions and outpatient intravenous antibiotic courses.⁵⁰ None of the patients developed diabetes mellitus during treatment with rhGH.^{50,51} These studies suggest a potential role for short-term treatment with rhGH in those children with severe growth impairment in order to minimize any rapid deterioration in lung disease. The potential long-term benefits of rhGH treatment on body composition, bone density, adult height, quality of life and survival, as well as cost and safety, particularly for glucose tolerance, have yet to be evaluated in patients with CF.

MANAGEMENT OF DELAYED PUBERTY

Delayed puberty is diagnosed on the basis of a short adolescent with a relatively short spine, delayed puberty and delayed bone age. Understandably it can arouse considerable anxiety, but intensive investigations are not required. The most important aspects of management are explanation and reassurance, particularly about sexual drive and function. For male patients with major psychological differences, treatment with low dose testosterone for 3–6 months is effective in advancing secondary sex characteristics and the growth spurt. The treatment does not enhance adult height but is safe in that it does not compromise final height.⁵³

CONCLUSIONS

The assessment of growth in children with CF is a valuable guide to well being, adverse clinical events and response to treatment. Serial records of height/length and weight plotted on standard distance charts are most useful in routine practice as they indicate the current state as well as the child's previous pattern of growth. All measurements need to be taken with accurate equipment and using correct techniques.

Compared to the normal population, patients with CF have poor growth from birth until adulthood. The growth impairment is more severe during adolescence and is associated with a delay in skeletal maturation and onset of puberty. For patients with CF, the issues arising from impaired growth are not merely aesthetic ones but pertain to physical health, survival and effectiveness of treatment. The major factors that adversely affect growth are undernutrition, chronic inflammation, diabetes mellitus,

liver disease and corticosteroid treatment. It is likely that these factors attenuate the functional integrity of the GH/IGF-I axis through complex interactions and negatively influence the neuroendocrine responses that initiate puberty.

Recent studies suggest a potential role for short-term treatment with rhGH in those children with severe growth impairment in order to improve growth and slow disease progression. However, the potential long-term benefits of rhGH treatment on body composition, bone density, adult height, quality of life and survival, as well as cost and safety, particularly for glucose tolerance, have yet to be evaluated in patients with CF.

REFERENCES

- Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 1995;**73**:17–24
- Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. *Arch Dis Child* 1966;**41**:613–35
- Sinaasappel M, Stern M, Littlewood J, *et al.* Nutrition in patients with cystic fibrosis: a European Consensus. *J Cystic Fibrosis* 2002;**1**:51–75
- Boyer PH. Low birth weight in fibrocystic disease of the pancreas. *Pediatrics* 1955;**16**:778
- Hsia DY. Birth weight in cystic fibrosis of the pancreas. *Ann Hum Genet* 1959;**23**:289–95
- Haeusler G, Frisch H, Waldhor T, Gotz M. Perspectives of longitudinal growth in cystic fibrosis from birth to adult age. *Eur J Pediatr* 1994;**153**:158–63
- Lai HC, Kosorok MR, Sondel SA, *et al.* Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: evaluation of various criteria used to identify malnutrition. *J Pediatr* 1998;**132**:478–85
- Sproul A, Huang N. Growth patterns in children with cystic fibrosis. *J Pediatr* 1964;**65**:664–76
- Karlberg J, Kjellmer I, Kristiansson B. Linear growth in children with cystic fibrosis: I. Birth to 8 years of age. *Acta Paediatr Scand* 1991;**80**:508–14
- Morison S, Dodge JA, Cole TJ, *et al.* Height and weight in cystic fibrosis: a cross sectional study. *Arch Dis Child* 1997;**77**:497–500
- Farrell PM, Kosorok MR, Rock MJ, *et al.* Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics* 2001;**107**:1–13
- Barkhouse LB, Fahey J, Gillespie CT, Cole DE. Quantitating the effect of cystic fibrosis on linear growth by mathematical modelling of longitudinal growth curves. *Growth Devel Aging* 1989;**53**:185–90
- Nir M, Lannig S, Johansen HK, Koch C. Long-term survival and nutritional data in patients with cystic fibrosis treated in a Danish centre. *Thorax* 1996;**51**:1023–7
- Byard PJ. The adolescent growth spurt in children with cystic fibrosis. *Ann Hum Biol* 1994;**21**:229–40
- Johannesson M, Gottlieb C, Hjelte L. Delayed puberty in girls with cystic fibrosis despite good clinical status. *Pediatrics* 1997;**99**:29–34
- Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;**41**:583–91
- Shwachman H, Kulczycki L. Long-term study of one hundred five patients with cystic fibrosis. *Am J Dis Child* 1958;**96**:6–15
- Moshang T, Holsclaw DS. Menarchal determinants in cystic fibrosis. *Am J Dis Child* 1980;**134**:1139–42

- 19 Mitchell-Heggs P, Mearns M, Batten JC. Cystic fibrosis in adolescents and adults. *Q J Med* 1976;**179**:479–504
- 20 Stern RC, Beat TF, Doershuk CF, *et al*. Course of cystic fibrosis in 95 patients. *J Pediatr* 1976;**89**:406–11
- 21 Collins CE, MacDonald-Wicks L, Rowe S, O'Loughlin EV, Henry RL. Normal growth in cystic fibrosis associated with a specialised centre. *Arch Dis Child* 1999;**81**:241–6
- 22 Gaskin KJ, Waters DL, Baur LA, Soutter VL, Gruca MA. Nutritional status, growth and development in children undergoing intensive treatment for cystic fibrosis. *Acta Paediatr Scand* 1990;**366**(suppl):106–10
- 23 Shepherd R, Cooksley WGE, Coole WDD. Improved growth and clinical, nutritional and respiratory changes in response to nutritional therapy in cystic fibrosis. *J Pediatr* 1980;**97**:351–7
- 24 McNaughton SA, Stormont DA, Shepherd RW, Francis PWJ, Dean B. Growth failure in cystic fibrosis. *J Paediatr Child Health* 1999;**35**:86–92
- 25 Lai HC, Kosorok MR, Laxova A, Davis LA, FitzSimmon SC, Farrell PM. Nutritional status of patients with cystic fibrosis with meconium ileus: a comparison with patients without meconium ileus and diagnosed early through neonatal screening. *Pediatrics* 2000;**105**:53–61
- 26 Kerem E, Corey M, Gold R, Levison H. Pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonisation with *Pseudomonas aeruginosa*. *J Pediatr* 1990;**116**:714–19
- 27 Del Pin CA, Czyrko C, Ziegler MM, Scanlin TF, Bishop HC. Management and survival of meconium ileus: a 30-year review. *Ann Surg* 1992;**215**:179–85
- 28 Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of menarche. *Arch Dis Child* 1971;**46**:695–701
- 29 Arrigo T, Rulli I, Lucanto C, Lombardo M, Miceli M, De Luca F. Analysis of the factors influencing menarcheal age in cystic fibrosis. *Horm Res* 2002;**58**(suppl 2):38
- 30 Greco L, Santamaria F, Salvatore D, de Ritis G. Growth dynamics in cystic fibrosis. *Acta Paediatr* 1993;**82**:254–60
- 31 Pamacku A, Bush A, Buchdahl R. Effects of *Pseudomonas aeruginosa* colonization on lung function and anthropometric variables in children with cystic fibrosis. *Pediatr Pulmonol* 1995;**19**:10–15
- 32 Laursen EM, Lanng S, Rasmussen MH, Koch C, Skakkebaek NE, Müller J. Normal spontaneous and stimulated GH levels despite decreased IGF-I concentrations in cystic fibrosis patients. *Eur J Endocrinol* 1999;**140**:315–21
- 33 Taylor AM, Bush A, Thomson A, *et al*. Relation between insulin-like growth factor-I, body mass index, and clinical status in cystic fibrosis. *Arch Dis Child* 1997;**76**:304–9
- 34 De Benedetti F, Alonzi T, Moretta A, *et al*. Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. *J Clin Invest* 1997;**99**:643–50
- 35 De Benedetti F, Meazza C, Martini A. Role of interleukin-6 in growth failure: an animal model. *Hormone Res* 2002;**58**(suppl 1):24–7
- 36 Nixon LS, Yung B, Bell SC, Elborn JS, Shale DJ. Circulating immunoreactive interleukin-6 in cystic fibrosis. *Am J Respir Crit Care Med* 1998;**157**:1764–9
- 37 Suter S, Schaad UB, Roux-Lombard P, Girardin E, Grau G, Dayer JM. Relation between tumor necrosis factor- α and granulocyte elastase- α 1-proteinase inhibitor complexes in plasma of patients with cystic fibrosis. *Am Rev Respir Dis* 1989;**140**:1640–4
- 38 Tirakitsontorn P, Nussbaum E, Moser C, Hill M, Cooper DM. Fitness, acute exercise, and anabolic and catabolic mediators in cystic fibrosis. *Am J Respir Crit Care Med* 2001;**164**:1432–7
- 39 Ripa P, Robertson I, Cowley D, Harris M, Masters IB, Cotterill AM. The relationship between insulin secretion, the insulin-like growth factor axis and growth in children with cystic fibrosis. *Clin Endocrinol* 2002;**56**:383–9
- 40 Poretsky L, Kalin MF. The gonadotropic function of insulin. *Endocr Rev* 1987;**8**:132–41
- 41 Terasawa E, Fernandez DL. Neurobiological mechanisms of the onset of puberty in primates. *Endocr Rev* 2001;**22**:111–51
- 42 Reiter EO, Stern RC, Root AW. The reproductive endocrine system in cystic fibrosis: 2. Changes in gonadotrophins and sex steroids following LHRH. *Clin Endocrinol* 1982;**16**:127–37
- 43 Bucuvalas JC, Chernauek SD, Alfaro MP, Krug SK, Ritschel W, Wilmott RW. Effect of insulinlike growth factor: 1. Treatment in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2001;**33**:576–81
- 44 Hardin DS, Sy JP. Effects of growth hormone treatment in children with cystic fibrosis: the National Cooperative Growth Study experience. *J Pediatr* 1997;**131**(suppl):S65–9
- 45 Hardin DS, Stratton R, Kramer JC, *et al*. Growth hormone improves weight velocity and height velocity in prepubertal children with CF. *Horm Metab Res* 1998;**30**:636–41
- 46 Alemzadeh R, Upchurch L, McCarthy V. Anabolic effects of growth hormone treatment in young children with cystic fibrosis. *J Am Coll Nutr* 1998;**17**:419–24
- 47 Huseman CA, Colombo JL, Brooks MA, *et al*. Anabolic effect of biosynthetic growth hormone in cystic fibrosis patients. *Pediatr Pulmonol* 1996;**22**:90–5
- 48 Sachey AH, Taylor CJ, Barraclough M, *et al*. Growth hormone as a nutritional adjunct in CF: results of a pilot study. *J Human Nutrition Dietet* 1995;**8**:185–91
- 49 Schnabel D, Staab D, Tacke A, *et al*. Effects of GH treatment on whole body protein turnover and body composition in patients with CF. *Hormone Res* 1997;**48**(suppl):368A
- 50 Hardin DS, Ellis KJ, Dyson M, Rice J, McConnell R, Seilheimer DK. Growth hormone improves clinical status in prepubertal children with cystic fibrosis: results of randomized controlled trial. *J Pediatr* 2001;**139**:636–42
- 51 Hutler M, Schnabel D, Staab D, Tacke A, Wahn U, Boning D, Beneke R. Effect of growth hormone on exercise tolerance in children with cystic fibrosis. *Med Sci Sports Exercise* 2002;**34**:567–72
- 52 Hardin DS, Ellis KJ, Dyson M, Rice J, McConnell R, Seilheimer DK. Growth hormone decreases protein catabolism in children with cystic fibrosis. *J Clin Endocrinol Metab* 2001;**86**:4424–8
- 53 Landon C, Rosenfeld RG. Short stature and pubertal delay in male adolescents with cystic fibrosis. Androgen treatment. *Am J Dis Child* 1984;**138**:388–91